Molecular Profiling of HNSCC Outcomes in Python

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Head & Neck Squamous Cell Carcinoma

- **"Head & Neck":** anatomic site
  - Oral cavity (mouth)
  - Pharynx (throat): oropharynx, hypopharynx
  - Larynx (voice box)
- **"Squamous Cell":** flat microscopic appearance of cell of origin
- **"Carcinoma":** cancer of mucosal lining (epithelium)
- **Epidemiology**
  - 6th leading cancer by incidence worldwide
  - Annually, 50,000 new cases in US and 500,000 worldwide

Goals of Staging

- Support the planning of treatment
- Give some indication of prognosis
- Assist in evaluating treatment results
- Allow unambiguous exchange of information between centers
- Further the investigation of human cancer
- Support cancer control activities

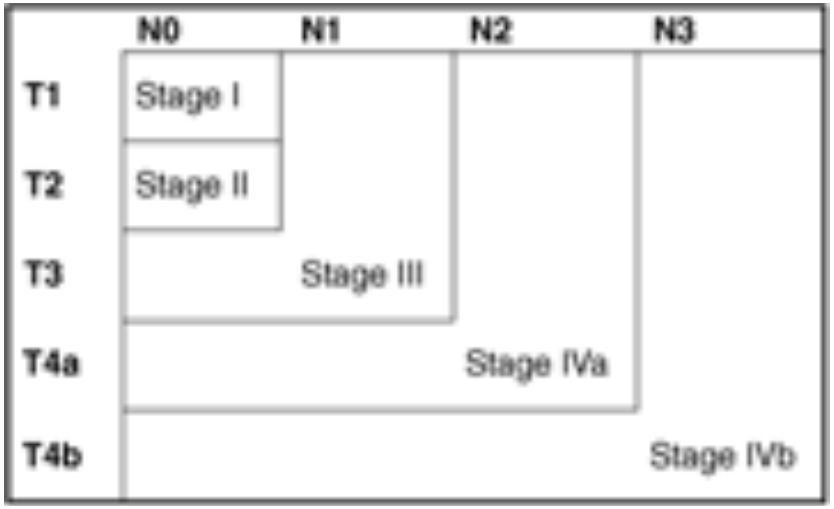
HNSCC Staging (Oral Cavity)

T - Tumor	
T1	Tumor < 2cm diameter
T2	Tumor 2-4cm diameter
T3	Tumor > 4cm diameter
T4a	Tumor invades bone, deep muscles of tongue, maxillary sinus, skin
T4b	Tumor invades masticator space or skull base or encases carotid artery

N - Node	
N0	No palpable nodes
N1	Single ipsilateral node < 3cm diameter
N2	Multiple ipsilateral nodes < 6cm diameter, or contralateral node(s) < 6cm diameter
N3	Node(s) > 6cm diameter

M - Metastasis	
M0	No distant metastasis
M1	Clinical/radiographic metastasis

Aggregate Clinical Stage



Properties of Staging Systems

- **Hazard Consistency:** Similar survival rates of patients within a given stage
- **Hazard Discrimination:** Different survival rates of patients between stages
- **Outcome Prediction:** Accurate prediction of cure following standard of care treatment
- **Balanced Distribution:** Balanced distribution of patients across stages

Poor Performance of TNM Staging System

	Oral Cavity	Oro-pharynx	Hypo-pharynx	Larynx	Perfect
Hazard Consistency	4.9%	5.1%	5.8%	1.9-2.9%	0%
Hazard Discrimination	0.44	0.39	0.39	0.42-0.47	1.00
Outcome Prediction	23.7%	11.4%	11.0%	19.3-19.6%	100%
Balanced Distribution	68%	57%	71%	63-66%	0%

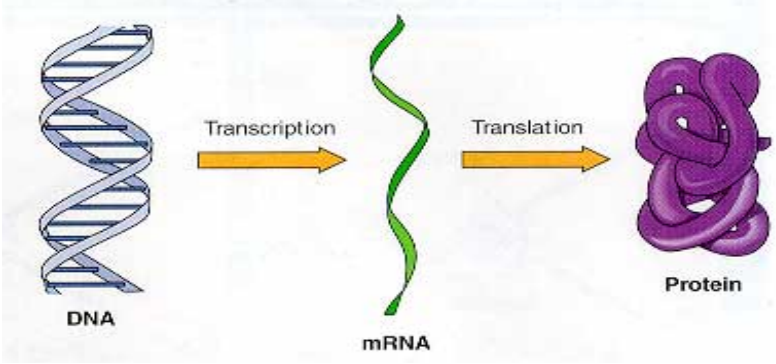
- **HC:** Average survival difference between TNM subgroups and corresponding stage group (0% is perfect)
- **HD:** Average of terms assessing even spacing of survival curves and width of survival difference spanned by scheme (1.00 is perfect)
- **OP:** Percent variance in survival outcomes explained (100% is perfect)
- **BD:** Percent average deviation from distribution with equal numbers of cases in each group (0% is perfect)

Shortcomings of TNM Staging

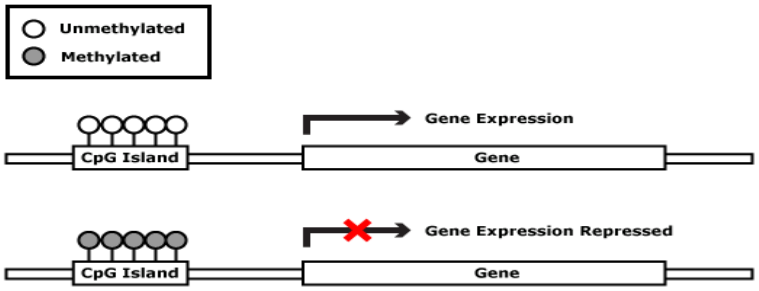
- TNM largely dependent on **pathologic staging**
  - pTNM not available when treating with non-surgical approaches
  - cTNM is not predictive of outcomes following nonsurgical treatment
- TNM accounts only for **variance based on anatomic extent of tumor**
  - Assumption: Temporal progression from primary site to regional lymphatics to distant organs, with worsening prognosis
  - Sources of variance not accounted for
    - Host factors: HPV status, tobacco/EtOH use, immune status, comorbidity
    - Gross tumor factors: tumor volume, vascular/perineural invasion, depth of invasion (e.g., deeply infiltrating tongue tumors have worse prognosis within a T stage), exo- vs. endophytic morphology
    - Microscopic tumor factors: cellular infiltrate and tumor grade
    - **Molecular and genetic factors**

Basic Genetic Abnormalities

Central Dogma



Promoter Methylation



- DNA abnormalities
  - **Mutations:** changes in the primary sequence (point, indel)
  - **Copy number variation:** deletion or replication of large DNA segments
  - **Methylation:** addition of CH_3 groups to CpG islands in promoter regions decreases expression
- RNA/protein abnormalities resulting from DNA abnormalities
  - **mRNA expression levels**
  - **Protein levels**
  - **Protein activity:** may be altered by abnormal levels or structure

Resources

- **The Cancer Genome Atlas (TCGA)**
  - Overview of TCGA
    http://cancergenome.nih.gov/cancersselected
  - Downloading the Data
    https://tcga-data.nci.nih.gov/tcga/dataAccessMatrix.htm
- **Supplementary Resources**
  - Sanger Institute
    http://www.sanger.ac.uk/research/projects/cancergenome/
  - Biological Annotation
    http://www.pantherdb.org/